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Synthesis of the First Calix[6]crypturea via a Versatile Tris-azide Precursor

Mickaël Ménand and Ivan Jabin*

Laboratoire de Chimie Organique, Université Libre de Bruxelles (U.L.B.), Avenue F. D. Roosevelt 50, CP160/06, B-1050 Brussels, Belgium

ijabin@ulb.ac.be

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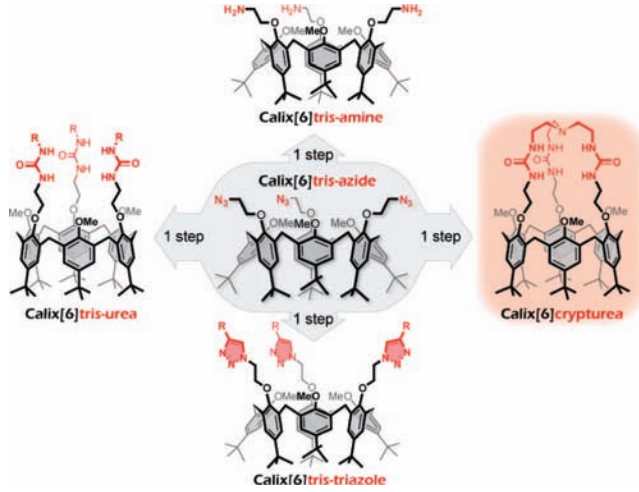
ABSTRACT



Various nitrogenous calix[6]arene based receptors have been synthesized in one step from a new C_{3v} symmetrical calix[6]arene intermediate decorated with azido groups. Hence, the first calix[6]crypturea has been obtained in high yield through a unique one-pot process consisting of a domino Staudinger/aza-Wittig reaction followed by a [1 + 1] macrocyclization reaction with a tripodal amine. The conformational properties and some of the host−guest properties of the new calix[6]arene derivatives have been studied by NMR spectroscopy.

Calixarenes are intensively studied as building blocks for the design of tailored molecular receptors.[1] In this context, C_{3v} symmetrical calix[6]arenes bearing a nitrogenous recognition site in close proximity to the hydrophobic cavity are particularly attractive because they can exhibit remarkable host−guest properties toward charged or neutral species (Figure 1). Indeed, calix[6]arenes with three appended aza-heterocyclic ligands at the level of the narrow rim were used for the elaboration of biomimetic metal complexes that can coordinate a variety of organic guests inside the cavity (i.e., *funnel complexes*).[2] The strong coordination of either anions or organic ion pairs (i.e., ammonium salts) was evidenced with heteroditopic calix[6]tris-urea based receptors.[3] When the ureido groups are introduced on the wide rim, pseudorotaxane-type complexes were produced.[4] The protonation of calix[6]tris-amines by carboxylic acids led to trications that assemble with the counteranions to form supramolecular ion-paired hosts for polar neutral molecules.[5] Calix[6]arenes possessing a tripodal aza-cryptand cap (i.e., polyamino or

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polyamido), namely, the calix[6]aza-cryptands, were shown to exhibit versatile host−guest properties toward either charged or neutral species thanks to the presence of the aza-cryptand cap that preorganizes the cavity and provides a tunable binding site.[6] The syntheses of all these calixarene based receptors required efficient methodologies for the introduction of nitrogenous functional groups on the phenolic positions. In particular, the grafting of a tripodal aza-cap through [1 + 1] macrocyclization reactions or of multiple functional groups in a single step must proceed in high yields. In this regard, we envisioned that a tris-azido-calixarene could constitute a valuable synthetic intermediate since the azide group offers a straigthforward access to a wide range of nitrogenous groups such as amine, imine, amide, urea, or triazoles.[7] Moreover, new classes of calix[6]aza-cryptands, such as calix[6]cryptureas, could be obtained through [1 + 1] macrocyclization reactions between a tris-azido-calixarene and tripodal aza-subunits. It is noteworthy that there is a growing interest in azido-calixarenes, as illustrated by their recent use in the syntheses of sophisticated architectures such as glycoclusters,[8] nanotubes,[9] and ditopic metal complexes.[10]

This paper describes the synthesis of the versatile intermediate calix[6]tris-azide **1** and the one-step access to various calixarene based receptors, one of them (i.e., the calix[6]crypturea) being obtained through a unique one-pot process involving a domino Staudinger/aza-Wittig type reaction followed by an efficient [1 + 1] macrocyclization reaction.

Calix[6]tris-azide **1** was synthesized in 93% yield by alkylation of the 1,3,5-tris-methoxycalix[6]arene ($X_6H_3Me_3$)[11] using an excess of 2-azidoethyl-4-methylbenzenesulfonate[12] (Scheme 1). Starting from this readily available precursor **1**, the one-step syntheses of various calixarene based receptors were tested. Our first aim was a more economical and shorter access to calix[6]tris-amine **2**, which is an important building block for the elaboration of multiple receptors.[3,5b−d,6b,c,e,g,13] Its previous three-step synthesis from $X_6H_3Me_3$ (79% overall yield) involved a costly reduction of a calix[6]tris-amide intermediate with a very large excess of BH_3·THF (30 equiv).[6e] The catalytic hydrogenation of calix[6]tris-azide **1** afforded calix[6]tris-amine **2** in almost quantitative yield (91% overall yield from $X_6H_3Me_3$). Reduction of compound **1** can also be performed in similar yield using Staudinger reduction conditions (PPh_3/H_2O).

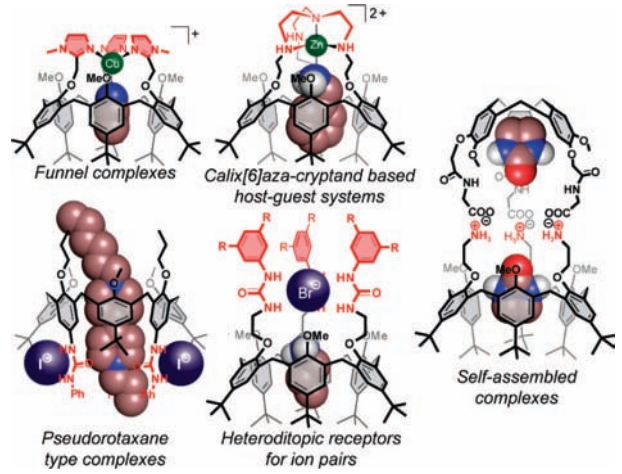

Figure 1. Examples of host−guest systems obtained with C_{3v} symmetrical calix[6]arenes bearing nitrogenous binding sites.[2−6]

Calix[6]tris-azide **1** proved to be an excellent candidate for the well-known copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition. Indeed, the reaction with either phenylacetylene or 2,2-dimethylbutyne provided the calix[6]tris-phenyltriazole **3** and calix[6]tris-*tert*-butyltriazole **4** in high yields. These two compounds constitute the first examples of C_{3v} symmetrical calix[6]arenes decorated with triazole subunits on the narrow rim. Considering the known coordinating properties of triazoles toward metal ions[10,14] or anions,[15] the calix[6]tris-triazoles **3** and **4** seem very promising for the design of new funnel complexes.

Calix[6]tris-urea receptors were also easily accessible from calix[6]tris-azide **1** using a domino Staudinger/aza-Wittig reaction (PPh_3/CO_2),[16] leading in situ to the reactive intermediate calix[6]tris-isocyanate, and a subsequent addition of an amine derivative. Thus, the use of either aromatic ($PhNH_2$) or aliphatic ($BnNH_2$) amines afforded the corresponding calix[6]tris-phenylurea **5** and calix[6]tris-benzylurea **6** in 82% and 79% yields, respectively. Finally, this remarkable one-pot process was attempted with a tripodal amine in order to develop the access to calix[6]cryptureas, a new family of calixcryptands that should possess reinforced properties toward anions and ion pairs in comparison to the less preorganized calix[6]tris-urea receptors. It is noteworthy

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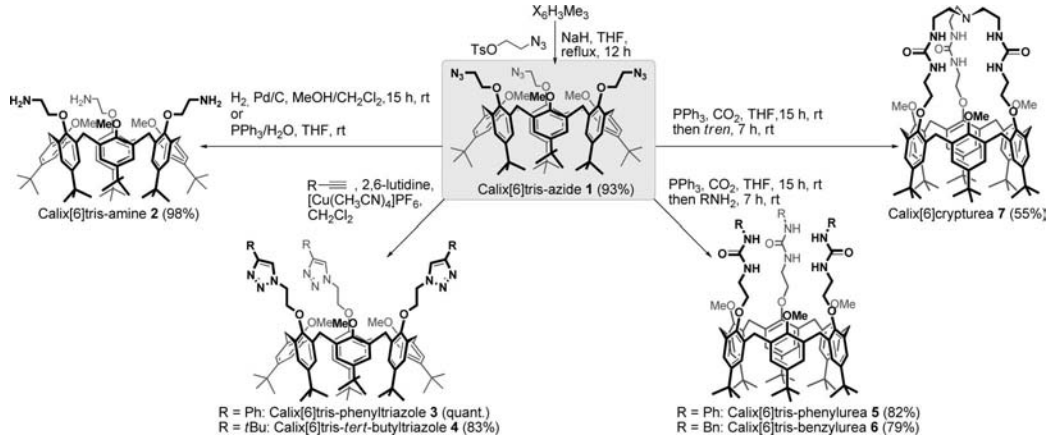
Scheme 1. Synthesis of Calix[6]tris-azide **1** and One-Step Access to Various Calixarene Based Receptors **2**−**7**



that [1 + 1] macrocyclization reactions between tripodal partners have never been achieved through this one-pot process,[17] and only few examples of tris-urea cryptands have been reported in the literature.[4b,18] Thus, the domino Staudinger/aza-Wittig procedure followed by the addition of 1 equiv of tris(2-aminoethyl)amine (tren) led to calix[6]crypturea **7** in 36% isolated yield from **1** (Table 1, entry 4). To estimate if an anion template effect could improve the yield of the macrocyclization, the reaction was carried out in presence of tetra-*n*-butylammonium (TBA^+) salts of the F^-, Cl^-, and Br^- anions (Table 1, entries 1−3). Except in the case of F^- that led to a complex mixture of products,[19] the presence of a halide did not affect significantly the reaction yield (Table 1, entries 2−4). In addition, the macrocyclization was carried out upon high dilution conditions. To our delight, the simultaneous addition of tren and calix[6]tris-isocyanate (freshly synthesized through the domino Staudinger/aza-Wittig process) over 12 h in THF (final concn = 2 mM) increased the yield of compound **7** to 55% (Table 1, entry 5).

Table 1. Influence of Concentration and Presence of Halides on the [1 + 1] Macrocylization Reaction

entry	X^{-a}	concn (mM)[b]	yield of **7** (%)[c]
1	F^-	20	nd[d]
2	Cl^-	20	34
3	Br^-	20	38
4		20	36
5		2	55

[a] TBA^+ salts were used. [b] Concentration of **1** and tren. [c] Isolated yields after FC purification. [d] Not detected.

The conformational properties of all of the new compounds **1**, **3**, **4**, **6**, and **7** were studied by NMR spectroscopy. In $CDCl_3$, **1**, **3**, and **4** displayed a C_{3v} symmetrical major flattened cone conformation ($\Delta\delta_{tBu} > 0.31$ ppm) with the OMe groups directed toward the inside of the cavity (δ_{OMe} = 2.63, 2.45, and 2.19 ppm, respectively), the bulkier azide and triazole groups being expelled from the cavity (Scheme 1).[20] In contrast, calix[6]tris-benzylurea **6** adopts a solvent-dependent cone conformation. Indeed, while a broad C_{3v} symmetrical NMR spectrum characteristic of a major straight cone conformation was observed in $CDCl_3$ ($\Delta\delta_{tBu} = 0.14$ ppm, $\delta_{OMe} = 3.12$ ppm), spectra recorded in competing solvent (either CD_3OD or acetone-d_6) led to sharper C_{3v} symmetrical patterns typical of flattened cone conformations with the OMe groups pointing inside the cavity ($\delta_{OMe} = 2.31$ and 2.47 ppm, respectively). This conformational flip of the aromatic units indicates the presence of an intramolecular hydrogen bonding network between the urea groups in non competing solvents.[21] In the case of the calix[6]crypturea **7**, a C_{3v} symmetrical straight cone conformation was observed either in competing (MeOD) or non-competing solvents ($CDCl_3$, see Figure 2) ($\Delta\delta_{tBu} = 0.15$ and 0.16 ppm, respectively). This different conformational behavior, as compared to **6**, is clearly due to the rigid covalent cap that prevents the expulsion of the urea groups of **7** in protic

(17) However, polyazido intermediates have been already involved in [1 + 1] macrocyclization reactions, leading either to tris-imine, tris-phosphazide, or tris-triazole derivatives; see, respectively: ref 9. Alajarín, M.; Molina, P.; López-Lázaro, A.; Foces-Foces, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 67–70. Morales-Sanfrutos, J.; Ortega-Muñoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7772–7774. For macrocyclization reactions between polyamines and calix[4]arenes, see:Hamdi, A.; Lee, Y. H.; Kim, Y.; Kusumahastuti, D. K. A.; Ohto, K.; Abidi, R.; Vicens, J. *Tetrahedron Lett.* **2009**, *50*, 540–543, and references therein.

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(19) The desired compound **7** was not detected on the ^1H NMR spectrum of the crude material.

(20) The spectra of **3** and **4** also show a minor C_s symmetrical species consistant with the 1,2,3-alternate conformation. This conformer is often observed with derivatives of $X_6H_3Me_3$ bearing bulky groups. See:van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken, S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 5814–5822.

(21) Similar conformational properties were observed for **5**. See ref 3.

solvents. This rigidification of the structure was also demonstrated through a VTNMR study (from 258 to 328 K), which showed that the conformation of **7** was only slightly affected by the temperature.[22] Moreover, the $ArCH_2$ signals appeared as a sharp pair of doublets over the whole temperature range, indicating that the aza-cap completely prevents the cone−cone interconversion.

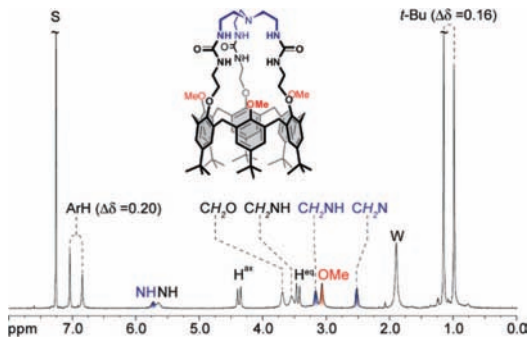

Figure 2. ^1H NMR spectrum ($CDCl_3$, 300 MHz, 298 K) of **7**. W = water, S = solvent.

Finally, the ability of calix[6]tris-ureas **5** and **6** to bind an organic ion pair (i.e., $PrNH_3^+Br^-$) in $CDCl_3$ was compared. First, ^1H NMR titration of compound **6** with TBA^+Br^- clearly showed H-bonding interactions between the anion and the urea groups of **6** since a strong downfield shift of the NH protons was observed.[23] Monitoring of the chemical shift variation of the OMe groups, which undergo a shielding effect upon complexation, afforded an association constant $K = 10\ M^{-1}$.[22] Thus, as compared to **5** ($K = 160\ M^{-1}$), calix[6]tris-urea **6** displays a much weaker ability to complex bromide, a priori due to the decrease of the urea acidity and the increase of steric hindrance close to the binding site.

Whereas the ^1H NMR spectrum of **6** remained unchanged upon addition of 1 equiv of propylammonium picrate ($PrNH_3^+Pic^-$), the subsequent addition of 1 equiv of TBA^+Br^- led to two new species corresponding to the complexes **[6⊃Br$^-$]** and **[6⊃PrNH$_3^+$,Br$^-$]**.[24] Indeed, the

(22) See Supporting Information.
(23) The complexation process is fast on the NMR time scale.
(24) A ^1H VTNMR study of this mixture of complexes was undertaken between 258 and 328 K (see Supporting Information).

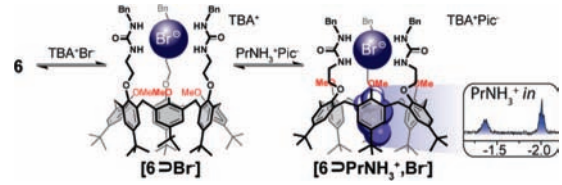

Figure 3. Host−guest properties of **6**. Inset: High-field region of the ^1H NMR spectrum ($CDCl_3$, 258 K) of **6** in presence of $PrNH_3^+Pic^-$ (1 equiv) and TBA^+Br^- (1 equiv).

presence of high-field signals showed the intracavity complexation of $PrNH_3^+$ simultaneously to the anion (Inset, Figure 3). This result highlights that the inclusion of $PrNH_3^+$ is directed by a cooperative two-step binding process with the anion playing the role of allosteric effector (Figure 3).[3] Furthermore, under these conditions (i.e., 1 equiv of $PrNH_3^+Pic^-$ and TBA^+Br^-), the fraction of included $PrNH_3^+$ was found to be 55%. This is significantly under the value measured for receptor **5** (i.e., 86%),[3] highlighting the importance of the nature of the urea substituent on the recognition process of the ion pair.

In conclusion, calix[6]tris-azide **1** constitutes a useful intermediate for the efficient one-step synthesis of a variety of nitrogenous calix[6]arene based receptors. Calix[6]crypturea **7** was obtained through a unique one-pot process consisting of a domino Staudinger/aza-Wittig reaction followed by a [1 + 1] macrocyclization reaction with a tripodal amine. The syntheses of diversely substituted calix[6]tris-urea derivatives gave some insights into the ion-pair recognition properties of these heteroditopic receptors, pointing out the crucial role of the urea substituent on the binding process.

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Supporting Information Available: General experimental methods; 1D, 2D NMR spectra of all new compounds; ^1H VTNMR and titration studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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